ORIGINAL INVESTIGATION

Response to a Second Single Antihypertensive Agent Used as Monotherapy for Hypertension After Failure of the Initial Drug

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Background: An important issue in clinical practice is how to treat patients whose blood pressure does not respond to the first antihypertensive drug selected.

Objective: To analyze the antihypertensive response of patients who had failed to achieve their diastolic blood pressure goal (<90 mm Hg at the end of 8 to 12 weeks of titration) with one of six randomly allocated drugs or placebo to the random allocation of an alternate drug.

Methods: We initially randomized 1292 men with diastolic blood pressure of 95 to 109 mm Hg to treatment with hydrochlorothiazide, atenolol, captopril, clonidine hydrochloride, diltiazem hydrochloride (sustained release), prazosin hydrochloride, or placebo. Of 410 men in whom initial treatment failed, 352 qualified for randomization to the alternate drug.

Results: Of the 352 patients, 173 (49.1%) achieved their goal diastolic blood pressure, in 133 (37.8%) the alternate drug failed, and 46 (13.1%) left the study for various reasons. Overall response rates were as follows: diltiazem, 63%; clonidine, 59%; prazosin, 47%; hydrochlorothiazide, 46%; atenolol, 41%; and captopril, 37%. The best response rate for patients in whom hydrochlorothiazide failed was achieved with diltiazem (70%); after atenolol failure, clonidine (86%); after captopril failure, prazosin (54%); after clonidine failure, diltiazem (100%); after diltiazem failure, captopril (67%); and after prazosin failure, clonidine (53%). The combined response rate for patients initially randomized to an active treatment was 76.0%, which is similar to that achieved by the combination of two drugs in previous studies.

Conclusions: We conclude that sequential single-drug therapy is a rational approach for treatment of hypertension in patients in whom initial drug therapy has failed.

(Arch Intern Med. 1995;155:1757-1762)

THE THEME of clinical trials conducted by the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents has been to provide data useful to health care providers for the treatment of hypertension in the office or clinic setting. A recent study of 1292 ambulatory men[1,2] was large enough to permit analysis of age-by-race interactions and to provide data suggesting how age and race might affect the response of patients to one of six classes of antihypertensive drugs. The overall response rate (diastolic blood pressure <90 mm Hg for two consecutive biweekly visits without drug intolerance) of the patients to initial single-drug therapy was high: 745 (57.7%) of 1292 reached this goal, and these patients entered a 1- to 2-year maintenance phase of the trial.

An important issue in clinical practice is how to treat patients whose blood pressure does not respond to the first drug selected. Strategies include stepped care (adding a second drug to the first)[3] and sequential therapy[4-9] (discontinuing the first drug and starting anew with an alternate drug). This single-drug therapy trial was designed to provide a substudy that would determine the success rate of sequential therapy. The objective was to analyze the response of patients who had failed to achieve their blood pressure goal with a first drug to the random allocation of an alternate drug. This article reports the results of that substudy.

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RESULTS

Of the 1292 men who initially qualified for randomization to one of the treatment

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PATIENTS AND METHODS

Detailed methods have been reported previously.[1] In brief, 1292 ambulatory men with diastolic blood pressure of 95 to 109 mm Hg after a 4- to 8-week washout period with placebo treatment were randomly allocated to double-blind treatment with one of six drugs or with placebo. The drugs and their potential doses during titration were as follows: atenolol, 25, 50, or 100 mg/d; captopril, 12.5, 25, or 50 mg twice daily; clonidine hydrochloride, 0.1, 0.2, or 0.3 mg twice daily; diltiazem hydrochloride (sustained release), 60, 120, and 180 mg twice daily; hydrochlorothiazide, 12.5, 25, or 50 mg/d; and prazosin hydrochloride, 2, 5, or 10 mg twice daily after 2 days of 1 mg twice daily, given to minimize first-dose syncopal reactions. The blinding system was double-dummy, so that each patient was given two bottles of medication at each visit. Only one contained active medication (or neither in the case of patients randomly allocated to placebo treatment). Patients who achieved goal diastolic blood pressure of less than 90 mm Hg without adverse drug effects at the end of 4 to 8 weeks were entered into a maintenance phase for at least 1 year. Those patients are the subject of the previous publication.[1] Patients who failed to achieve goal blood pressure were entered into a second placebo washout phase with visits every 2 weeks for a maximum of 8 weeks.

Patients qualified for the second drug titration if their blood pressure rose to baseline at or after the fourth week of the second washout period. This was done to eliminate any residual effects of the first drug. Safety criteria required discontinuation of patients from the trial if their blood pressure exceeded predefined limits (diastolic blood pressure >114 mm Hg on any one visit or >109 mm Hg on two consecutive visits, or systolic blood pressure >199 mm Hg on any one visit). Those patients who qualified were then treated with a randomly allocated alternate drug. The blind was maintained by issuing a new pair of drugs, of which only one was active. Placebo was not an option for this portion of the study, to prevent patients from being treated with placebo for an extended time. Dosages were titrated blindly every 2 weeks until the patient achieved goal blood pressure for 2 consecutive weeks without experiencing adverse effects. Patients who achieved goal blood pressure were discontinued from the study at that point and treated with open-label medication. Patients who failed to respond to this second attempt at single-drug therapy by 12 weeks entered a separate drug combination arm of the study.

The baseline blood pressure was calculated as the average of the six readings obtained in the last two clinic visits before randomization. Treatment blood pressure was calculated as the average of the six readings from the last two clinic visits of the titration period. Blood pressure readings were determined by trained observers with the use of standard sphygmomanometers. Readings were taken after the patient had been sitting for 5 minutes. Diastolic blood pressure was recorded as the disappearance of Korotkoff sounds (phase V).

Adverse drug reactions were analyzed by the study chairman without knowledge of the drug assignment. The significance of differences in treatment response rates was determined by a χ^2 test of homogeneity for a 2×6 contingency table. All results are reported according to an intention-to-treat analysis. SAS software was used for all analyses. A P value of .05 or less was interpreted as indicating statistical significance. All statistical tests were two tailed.

The protocol was approved by institutional review boards at each of the participating medical centers and by a central Cooperative Studies review committee.

arms, 537 either failed to achieve goal blood pressure or were disqualified from continuing in the study for other reasons. Of these, 410 agreed to continue into the washout phase, and 352 qualified for treatment with the alternate drug. Their baseline data (**Table 1**) do not reflect major differences between the subgroups. Of the 352 patients who entered this phase, 46 (13.1%) left or were removed from the study for various reasons, 173 (49.1%) achieved goal blood pressure, and 133 (37.8%) did not achieve goal blood pressure with the maximally tolerated dosage.

Table 2 displays the average reductions in systolic and diastolic blood pressure from the baseline and washout phases to the end of the titration phase for each of the sequential drugs. The washout blood pressures were not statistically significantly different from those at baseline. All six drugs achieved a statistically significant reduction from both the baseline and washout phases. There were no between-drug differences in the magnitude of diastolic blood pressure reduction. Clonidine achieved a significantly greater reduction in systolic blood pressure from baseline than atenolol did. Clonidine and hydrochlorothiazide achieved greater reduction of systolic pressure from washout than atenolol did.

Table 3 summarizes the results of treatment with the alternative drug for each initial drug treatment group. Subgroup analysis showed that 82 (54.0%) of 152 white patients responded to a second drug, as did 91 (46.4%) of 196 black patients. The response rate was 37.6% (59/157) for younger patients and 58.5% (114/195) for older patients. Age-by-race subgroups had small total numbers. The response rate was 38.5% (25/65) for younger whites, 37.8% (34/90) for younger blacks, 65.5% (57/87) for older whites, and 53.8% (57/106) for older blacks.

Captopril (6/11 [54.5%]) and clonidine (6/12 [50%]) had the highest response rates and hydrochlorothiazide (2/11 [18.2%]) the lowest for younger whites. Diltiazem (7/12 [58.3%]) had the highest and captopril (4/15 [26.7%]) and atenolol (6/22 [27.3%]) the lowest response rates for younger blacks. The response rates for older whites were high for prazosin (9/11 [81.8%]), clonidine (14/18 [77.8%]), atenolol (10/13 [76.9%]), and diltiazem (10/15 [66.7%]); rates were lower for hydrochlorothiazide (6/11 [54.5%]) and captopril (8/19 [42.1%]). For older blacks, the highest response rates were for diltiazem (15/21 [71.4%]), hydrochlorothiazide (15/23 [65.2%]), and clonidine (13/21 [61.9%]); atenolol (6/16 [37.5%]), prazosin (4/12 [33.3%]), and captopril (4/13 [30.8%]) were less effective.

Table 1. Baseline Characteristics of All Patients With Initial Treatment Failure and Their Age-Race Subgroups

	All Patients	Younger	Older	Whites	Blacks	Younger Whites	Younger Blacks	Older Whites	Older Blacks
No. (%) of patients*	352	157	195	152	196	65 (18.5)	90 (25.6)	87 (24.7)	106 (31.1)
Age, y (mean±SD)	58±10	50±8	66±4	59±9	59±11	51±7	49±8	65±4	66±4
Systolic blood pressure, mm Hg									
Mean±SD	155±14	150±13	158±14	155±14	154±14	152±14	149±12	157±14	159±14
No. (%) ≥160	129 (36.6)	39 (24.8)	90 (46.2)	62 (40.8)	65 (33.2)	21 (32.3)	18 (20.0)	41 (47.1)	47 (44.3)
No. (%) 140-159	163 (46.3)	79 (50.3)	84 (43.1)	66 (43.4)	96 (49.0)	30 (46.2)	48 (53.3)	36 (41.4)	48 (45.3)
Diastolic blood pressure, mm Hg									
Mean±SD	101±3	101±3	100±3	100±3	101±4	100±3	101±3	100±3	101±4
No. (%) 100-109	181 (51.4)	89 (56.7)	92 (47.2)	74 (48.7)	105 (53.6)	34 (52.3)	53 (58.9)	40 (46.0)	52 (49.1)
No. (%) 95-99	155 (44.0)	61 (38.9)	94 (48.2)	65 (42.8)	88 (44.9)	24 (37.0)	37 (41.1)	41 (47.1)	51 (48.1)
Heart rate, beats/min	75±11	75±11	74±11	75±12	74±11	76±12	75±10	74±11	74±11
Body mass index†	29±5	29±5	29±5	30±5	29±5	29±5	29±5	30±5	29±5
Cigarette smoking, No. (%)									
Current	106 (30.1)	57 (36.3)	49 (25.1)	30 (19.7)	76 (38.8)	16 (24.6)	41 (45.6)	14 (16.1)	35 (33.0)
Former	152 (43.2)	54 (34.4)	98 (50.3)	73 (48.0)	78 (39.8)	25 (38.5)	29 (32.2)	48 (55.2)	49 (46.2)
Never	94 (26.7)	46 (29.3)	48 (24.6)	49 (32.2)	42 (21.4)	24 (36.9)	20 (22.2)	25 (28.7)	22 (20.8)
Alcohol consumption, No. (%)									
No or <1 drink/d	280 (79.5)	122 (77.7)	158 (81.0)	115 (75.7)	161 (82.1)	48 (73.8)	72 (80.0)	67 (77.0)	89 (84.0)
1-3 drinks/d	60 (17.0)	28 (17.8)	32 (16.4)	30 (19.7)	30 (15.3)	12 (18.5)	16 (17.8)	18 (20.7)	14 (13.2)
>3 drinks/d	12 (3.4)	7 (4.5)	5 (2.6)	7 (4.6)	5 (2.6)	5 (7.7)	2 (2.2)	2 (2.3)	3 (2.8)
No. (%) antihypertensive treatment at screening	269 (76.4)	114 (72.6)	155 (79.5)	112 (73.7)	153 (78.1)	43 (66.2)	69 (76.7)	69 (79.3)	84 (79.2)

*Four patients were Asian. Their data were not analyzed separately.
†(Weight in kilograms)/(height in meters)^2.

Table 2. Average Reductions in Blood Pressure From Baseline and Washout to the End of the Sequential Drug Titration Phase

		Mean±SD, mm Hg				
Sequential Drug	N	Baseline	Washout	End of Titration	Reduction From Baseline	Reduction From Washout
Diastolic Blood Pressure						
Hydrochlorothiazide	60	100.4±3.3	100.1±4.0	90.3±6.2	10.1±6.1	9.8±5.5
Atenolol	58	100.3±3.3	99.5±4.5	91.6±7.6	8.7±7.0	7.9±7.2
Captopril	59	100.2±3.1	99.6±4.4	91.1±6.6	9.1±6.5	8.4±6.4
Clonidine hydrochloride	67	100.7±3.5	100.6±4.5	89.5±8.6	11.2±8.1	11.1±7.8
Diltiazem hydrochloride (sustained release)	57	101.1±3.8	99.9±4.3	88.7±7.1	12.4±7.3	11.2±6.9
Prazosin hydrochloride	48	100.3±3.4	99.8±5.8	90.9±7.4	9.4±6.8	8.9±6.1
Systolic Blood Pressure						
Hydrochlorothiazide	60	152.8±15.6	152.4±13.8	138.8±12.5	14.0±13.2	13.6±10.7
Atenolol	58	155.4±13.2	152.9±13.2	146.8±17.2	8.6±12.9*	6.1±11.7†
Captopril	59	155.3±13.3	153.7±13.7	144.0±16.0	11.2±12.6	9.7±11.7
Clonidine	67	156.5±13.1	158.4±13.4	140.5±13.7	16.0±14.0*	17.9±12.9‡
Diltiazem	57	154.3±14.9	153.6±13.1	142.4±13.4	11.9±11.5	11.2±12.0
Prazosin	48	154.2±14.9	153.0±15.3	144.9±15.5	9.3±13.3	8.2±11.8

*Clonidine and atenolol were different from each other.
†Atenolol was different from clonidine and hydrochlorothiazide.
‡Clonidine was different from all drugs except hydrochlorothiazide.

The **Figure** compares the overall end-titration response rates for the initial drug and the sequential drug. The hierarchy of response rates for the sequential drugs was similar to that for the initial drugs. Atenolol, however, fell from the third position to fifth.

The dose of drug required to achieve response followed the pattern observed in the original study. Sixty-one percent of the 29 responses to hydrochlorothiazide were achieved at 12.5 mg (seven patients) or 25 mg (10 patients). Three adverse drug reactions that required withdrawal from the study were associated with 25-mg (one case) or 50-mg (two cases) doses. For atenolol, 11 (46%) of the 24 responses were achieved with 25 mg. The two adverse drug reactions were at 25 and 50 mg. For captopril, 12 (55%) of the 22 responders required 100 mg, but the single withdrawal for an adverse drug reaction occurred at 25 mg. For clonidine, 17 (43%) of the 40 responders required 0.6 mg. There were nine withdrawals caused by adverse drug reactions: two with 0.2 mg, five with 0.4 mg, and two with 0.6 mg. Of the 36 responders

Table 3. Response to a Second Single Antihypertensive Drug After Failure of Initial Monotherapy*

Initial Drug and Race or Age Subgroup	Sequential Single Drug, No. (%)						Total, No. (%)†	P
	Hydrochlorothiazide	Atenolol	Captopril	Clonidine Hydrochloride	Diltiazem Hydrochloride (Sustained Release)	Prazosin Hydrochloride		
Hydrochlorothiazide	...	5/11	5/14	8/15	7/10	3/9	28/59 (47.5)	.231
White		1/3	4/8	7/8	2/3	2/6	16/28 (57.1)	.251
Black		4/8	1/5	1/6	5/7	1/3	12/29 (41.4)	.250
Younger		2/7	3/6	1/7	3/4	1/7	10/31 (32.3)	.176
Older		3/4	2/8	7/8	4/6	2/2	18/28 (64.3)	.072
Atenolol	5/12	...	1/6	6/7	6/13	0/4	18/42 (42.9)	.039
White	1/3		1/3	4/4	3/6	0/2	9/18 (50.0)	.155
Black	4/9		0/3	2/3	3/7	0/2	9/24 (37.5)	.359
Younger	1/4		0/4	2/2	1/4	0/2	4/16 (25.0)	.092
Older	4/8		1/2	4/5	5/9	0/2	14/26 (53.8)	.437
Captopril	6/14	4/11	...	3/7	5/12	6/11	24/55 (43.6)	.938
White	1/4	2/4		2/4	2/6	1/2	8/20 (40.0)	.924
Black	5/9	2/7		1/3	3/6	5/9	16/34 (47.1)	.785
Younger	1/2	0/2		2/5	3/6	3/5	9/20 (45.0)	.695
Older	5/12	4/9		1/2	2/6	3/6	15/35 (42.9)	.982
Clonidine	6/12	2/8	2/6	...	3/3	4/9	17/38 (44.7)	.361
White	3/4	3/4	2/2		1/1	2/5	9/15 (60.0)	.393
Black	3/7	1/5	0/4		2/2	2/4	8/22 (36.4)	.146
Younger	2/7	1/4	0/3		2/2	2/6	7/22 (31.8)	.214
Older	4/5	1/4	2/3		1/1	2/3	10/16 (62.5)	.448
Diltiazem	4/11	0/3	4/6	1/6	...	1/4	10/30 (33.3)	.122
White	1/5	1/5	4/6	1/4		1/2	7/18 (38.9)	.439
Black	3/6	0/2	0/0	0/2		0/2	3/12 (25.0)	.261
Younger	0/6	0/3	2/2	1/6		1/2	4/19 (21.1)	.027
Older	4/5	0/0	2/4	0/0		0/2	6/11 (54.6)	.154
Prazosin	2/6	3/7	5/11	8/15	3/6	...	21/45 (46.7)	.952
White	0/3	0/3	2/5	2/4	1/2		5/14 (35.7)	.524
Black	2/3	3/7	3/6	6/11	2/4		16/31 (51.6)	.970
Younger	2/6	2/3	2/6	3/4	0/3		9/22 (40.9)	.276
Older	0/0	1/4	3/5	5/11	3/3		12/23 (52.2)	.235
Placebo	5/6	10/18	5/16	14/18	12/13	9/12	55/83 (66.3)	.010
White	2/3	2/3	1/6	4/6	5/6	8/9	28/39 (71.8)	.033
Black	3/3	2/9	4/10	10/12	7/7	1/3	27/44 (61.4)	.004
Younger	1/1	3/10	3/5	4/5	2/2	3/4	16/27 (59.3)	.227
Older	4/5	7/8	2/11	10/13	10/11	6/8	39/56 (69.6)	.003
Total‡	28/61 (45.9)	24/58 (41.4)	22/59 (37.3)	40/68 (58.8)	36/57 (63.2)	23/49 (46.9)	173/352 (49.1)	.033
White	8/22 (36.4)	8/22 (36.4)	14/30 (46.7)	20/30 (66.7)	14/24 (58.3)	14/26 (53.8)	82/152 (54.0)	.325
Black	20/37 (54.1)	12/38 (31.6)	8/28 (28.6)	20/37 (54.1)	22/33 (66.7)	9/23 (39.1)	91/196 (46.4)	.012
Younger	7/26 (26.9)	8/29 (27.6)	10/26 (38.5)	13/29 (44.8)	11/21 (52.4)	10/26 (38.5)	59/157 (37.6)	.401
Older	21/35 (60.0)	16/29 (55.2)	12/33 (36.4)	27/39 (69.2)	25/36 (69.4)	13/23 (56.5)	114/195 (58.5)	.063

*Response was defined as a diastolic blood pressure less than 90 mm Hg at end-titration. Significance of differences in treatment response rates was determined by a χ^2 test of homogeneity for a 2×6 contingency table.

†Number of patients who responded/number treated with the five alternative sequential drugs.

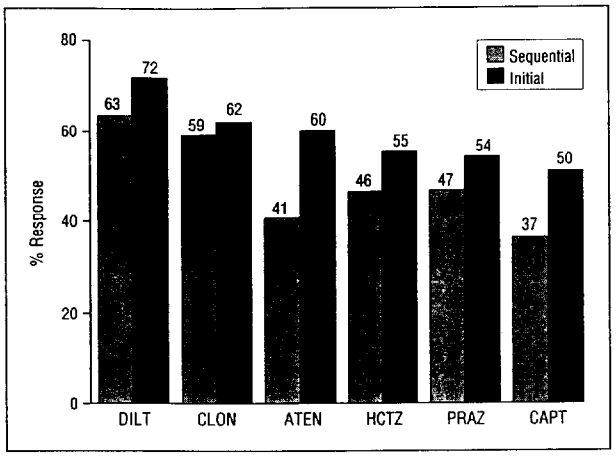
‡Number of patients who responded/number treated with each sequential drug.

to diltiazem, 11 (31%) required 240 mg and 19 (53%) required 360 mg. There were five withdrawals caused by adverse drug reactions: one with 120 mg and two each with 240 and 360 mg. Of the 23 responses to prazosin, six (26%) occurred at 4 mg, seven (32%) at 10 mg, and 10 (43%) at 20 mg. There was one withdrawal for an adverse drug reaction at 4 mg and five at 10 mg.

COMMENT

Numerous epidemiologic and clinical observations serve to support the heterogeneity of primary hypertension. Consequently, individual patients with similar degrees of hypertension (perhaps caused by a variety of mechanisms) may differ greatly in their response to particular antihypertensive drugs. It is often unclear which agent to select as single-drug therapy in a given patient. Our main study[1] provided a logical basis for initial drug selection based on antihypertensive efficacy and drug tolerance.

A common and important problem in the treatment of primary hypertension is how to treat patients in whom initial single-drug therapy with a given agent proves ineffective. Alternatives include (1) combination therapy using a stepped-care approach (adding a second drug to the first) and (2) sequential therapy (stopping the initial drug and beginning treatment with a second agent). The more traditional stepped-care approach has



Percentage response (diastolic blood pressure <90 mm Hg at the end of the titration period) achieved by each of the initial drugs compared with that achieved by each of the sequential single drugs. All of the patients who received the sequential drug had failed to achieve a response to an initial drug. DILT indicates diltiazem hydrochloride (sustained release); CLON, clonidine hydrochloride; ATEN, atenolol; HCTZ, hydrochlorothiazide; PRAZ, prazosin hydrochloride; and CAPT, captopril.

usually implied that if the first agent does not result in the achievement of goal blood pressure, then others would be added. The validity of such an approach has been demonstrated in a number of clinical settings, including such combinations as angiotensin-converting enzyme inhibitors with calcium-channel blocking agents,[10] thiazide diuretics with angiotensin-converting enzyme inhibitors[11] or β-blockers,[12] and α-blockers with angiotensin-converting enzyme inhibitors.[13] However, the addition of a second drug to an initial agent that is not working could potentially mean in some cases that patients are receiving one or more agents that are ineffective. One goal of long-term antihypertensive therapy is to give the fewest number of drugs needed to control blood pressure. With the introduction of numerous new antihypertensive agents, effective single-drug therapy for hypertension is now possible in a high percentage of patients.[1]

Our study provides data on sequential therapy in 352 patients whose blood pressure was not controlled with a randomly assigned initial antihypertensive agent and who were then randomly allocated to receive treatment with a second agent. The data suggest that sequential therapy is a rational approach to the treatment of patients whose blood pressure has not responded to a first agent. The response rate to a randomly assigned second drug for patients in whom active treatment initially failed was 43.9% (118/269), a number to be compared with the overall response rate to the first drug assigned of 61.8% (683/1105 patients allocated to active drug treatment). Excluding 52 patients who initially failed an active treatment and withdrew during the placebo washout phase, the combined response rate was 76.0% (801/1053). This is comparable with the results of other Veterans Affairs cooperative studies: 52% for propranolol alone, 81% for propranolol plus hydrochlorothiazide, 72% for propranolol plus hydralazine, and 88% for reserpine plus hydrochlorothiazide[14]; 49% for nadolol alone, 46% for bendroflumethiazide alone, and 85% for nadolol plus bendroflumethiazide[15]; 33% for captopril alone and 72% for captopril plus hydrochlorothiazide.[11] Our findings are also similar to those of a study in elderly patients in which response to hydrochlorothiazide alone was 50.4% to 58.5% and the results of the addition of a second drug were 85.3% for hydralazine, 81.7% for methyldopa, 76.9% for metoprolol, and 72.3% for reserpine.[16] Drug allocation for the initial and sequential drug in this study was entirely random, so that an even higher response rate might be expected if the drugs were selected on a rational basis.

Overall response rates seemed to differ among the randomly allocated second agents: diltiazem (63%), clonidine (59%), prazosin (47%), hydrochlorothiazide (46%), atenolol (41%), and captopril (37%). Response rates to the second agent were substantial in both black patients (46.4%) and white patients (54.0%). Younger patients (37.6%) did not seem to respond to a random second drug as well as older patients (58.5%); this was true for both younger blacks (37.8%) and younger whites (38.5%). However, it is difficult to draw conclusions regarding comparison of age-by-race response rates to the second agent; the number of patients allocated to each agent in each age-by-race group is small.

Our patient population was drawn from a pool of men with diastolic blood pressures in the range of 95 to 109 mm Hg, ie, patients with Joint National Committee V stage 1 (mild) and stage 2 (moderate) diastolic hypertension.[3] Drug response failures in our study were more likely if the baseline diastolic blood pressure was greater than 100 mm Hg. Patients with more severe degrees of hypertension may require combinations of two or more drugs, and other situations may arise in which discontinuation of the first drug is inadvisable.

As in the previous study, these drugs proved to be remarkably free from adverse drug reactions requiring withdrawal from the trial. The pattern of response was similar to that in the previous trial, suggesting that there is little or no systematic disadvantage to being exposed to a different second single-drug therapy.

We emphasize that these data are derived from a cohort of patients in whom therapy with an original randomly allocated drug failed. They cannot, therefore, be considered to be equivalent to the original group. All patients were men; these results might not be similar in women. Nevertheless, this group of patients corresponds to the frequently encountered clinical situation in which initial single-drug therapy has failed. Our results indicate that patients whose hypertension is resistant to one drug may be responsive to an alternate single drug. The addition of a second drug is not necessarily required. This supports the logic to sequential single-drug therapy as opposed to immediately adding a second drug.

Accepted for publication January 25, 1995.

This study was supported by the Cooperative Studies Program of the Department of Veterans Affairs Medical Research Service. We gratefully acknowledge the supply of drugs and their matching placebos by Ciba-Geigy Corp, Summit, NJ (hydrochlorothiazide), ICI Pharma, Wil-

The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents

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mington, Del (atenolol), Bristol-Myers Squibb, Wallingford, Conn (captopril), Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Conn (clonidine), Marion Merrell Dow Inc, Kansas City, Mo (diltiazem), and Pfizer Laboratories Division, New York, NY (prazosin). We also gratefully acknowledge a grant of unrestricted funds to Friends of Medical Research Inc by Marion Merrell Dow Inc.

Presented in part at the annual scientific meeting of the American Society of Hypertension, New York, NY, May 12, 1994.

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Printed and Published in the United States of America